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ORIGINAL ARTICLE



# Use of antihypertensive medication after ischemic stroke in young adults and its association with long-term outcome

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## ABSTRACT

**Background:** Knowledge on the use of secondary preventive medication in young adults is limited.

**Methods:** We included 936 first-ever ischemic stroke 30-day survivors aged 15–49, enrolled in the Helsinki Young Stroke Registry, 1994–2007. Follow-up data until 2012 came from Finnish Care Register, Statistics Finland, and Social Insurance Institution of Finland. Usage thresholds were defined as non-users, low (prescription coverage <30%), intermediate (30–80%) and high users (>80%). Adjusted Cox regression allowed assessing the association of usage with all-cause mortality and recurrent vascular events.

**Results:** Of our patients, 40.5% were non-users, 7.8% had low usage, 11.8% intermediate usage and 40.0% high usage. Median follow-up was 8.3 years. Compared to non-users, risk of mortality and recurrent stroke or TIA was lower for patients with low-intermediate (HR 0.40, 95% CI 0.22–0.65; HR 0.31, 95% CI 0.18–0.53) and high usage (HR 0.25, 95% CI 0.15–0.42; HR 0.30, 95% CI 0.19–0.46), after adjustment for confounders.

**Conclusions:** Use of antihypertensives was suboptimal in one-third of patients in whom antihypertensives were initially prescribed. Users were at lower risk of mortality and recurrent stroke or TIA compared to non-users.

## KEY MESSAGES

- The use of antihypertensive medication is suboptimal in one-third of patients in whom antihypertensive medication was initially prescribed after ischemic stroke at young age.
- The risk of mortality and recurrent stroke or TIA is lower for users of antihypertensive medication after ischemic stroke at young age compared to non-users, after adjustment for relevant confounders including pre-existing hypertension and prior use of antihypertensive medication.
- Specific guidelines on antihypertensive medication use after ischemic stroke at young age are lacking. However, our results may motivate doctors and patients in gaining better usage of antihypertensive medication, since better usage was associated with more favorable outcome in this study.

## ARTICLE HISTORY

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## KEYWORDS

Brain ischemia/drug therapy; follow-up studies; hypertension; recurrence; risk; stroke/drug therapy; young adults

## Introduction

Patients with an ischemic stroke (IS) at young age are known to be at a substantial long-term risk of recurrent vascular events and death. One out of three will be affected by recurrent vascular events and the risk of mortality is 4-fold of expected, even up to 10 years after the initial event [1–4]. Furthermore, the risk of recurrence is found to be true-to-type, with high risks of a recurrent IS in young IS patients [5]. As these

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diseases occur rather early in life, they incur high socioeconomic costs for both the individual and the society [6]. This warrants targeted aggressive secondary prevention.

Antihypertensive therapy is proven to reduce the rate of recurrent stroke, based on a number of randomized, placebo-controlled trials [7–9]. However, regular and lifelong use of antihypertensive medication in young adults is a particular challenge given the life-long need for medication use, altered self-identity, greater blood pressure variability compared to older adults and possible side effects of medication [10].

There are no studies using longitudinal data examining factors influencing use of antihypertensive medication or the association between the use of antihypertensive medication and recurrent vascular events after stroke at younger ages. Data regarding younger adults from randomized trials on antihypertensive medication is lacking since few young adults with IS have been included in these trials. Moreover, guidelines on secondary prevention after stroke are not specifically aimed at younger stroke patients.

In this study, we examined the association between the use of antihypertensive medication and mortality in young adults with IS, stratifying for etiologic subgroups. Secondary, we assessed the association between the use of antihypertensive medication and subsequent vascular events, including recurrent stroke or TIA and vascular events other than stroke.

## Methods

### Data availability statement

Data cannot be shared for both legal and ethical reasons. Data from Care Register for Health Care, the National Institute for Health and Welfare and Statistics Finland can only be used for the purpose stated in the license granted, scientific research on society by the license applicant, and can therefore not be shared with third parties. However, we carefully documented the data, methods and materials used to conduct the research in this article. If one wishes to perform scientific research and/or statistical surveys on society with the data, one could apply for a license from these institutions.

### Study population

The Department of Neurology, Helsinki University Hospital (HUH) has the only neurological emergency unit for a population of 1.6 million inhabitants. All 1008 consecutive patients aged 15–49 years with a first-ever IS treated in the Department of Neurology, Helsinki University Hospital, from January 1994 to May 2007, were identified from a prospective computerized hospital discharge database and were included in the Helsinki Young Stroke Registry (HYSR). History of prior stroke was based on medical records at the time of the initial data collecting process. We used the definition of stroke given by the WHO, but also included those patients with imaging-positive acute ischemic findings in the brain region appropriate to clinical presentation, even when the symptoms lasted less than 24 h [11,12].

### Baseline data

Baseline laboratory and other diagnostic tests have been described in full previously [11]. We performed computed tomography or magnetic resonance imaging for all patients. Hypertension was defined as treated hypertension or a history of hypertension according to the 2003 World Health Organization criteria [13]; systolic blood pressure (SBP) $\geq$140 mm Hg and/or diastolic blood pressure (DBP) $\geq$90 mmHg [11]. Baseline blood pressure values were recorded at admission and 24 h after admission, which are ought to be only slightly higher than pre-morbid blood pressure values [14]. We initially classified causes of stroke using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [15], with further modifications revealing specific underlying causes in the category of cardioembolism, using patient records, lab records and imaging studies. Cardioembolic strokes were divided into low-risk sources of cardioembolism, which included patent foramen ovale and/or sole atrial septal aneurysm, and high-risk sources of cardioembolism, which included all other causes [16]. Moreover, after introduction of criteria for embolic stroke of undetermined source (ESUS) [17], we identified ESUS patients among those with low-risk sources of cardioembolism and TOAST undetermined etiology [18]. Non-ESUS cryptogenic included patients with stroke with two or more causes identified, those with negative evaluation that did not fulfill ESUS criteria and patients with incomplete evaluation. Furthermore, we identified large-artery atherosclerosis (LAA), high-risk source of cardioembolism (CEH) and small-vessel occlusion (SVO) as "older-onset stroke causes" due to the increasing incidences of these causes of stroke with rising age [19], and other determined causes, ESUS and non-ESUS cryptogenic causes as "young-onset stroke causes", due to the particularly high incidences among younger patients. Stroke severity at

admission was assessed with National Institutes of Health Stroke Scale (NIHSS). We used patients' vocational status as a measure of socioeconomic status (SES). SES was defined as upper-white-collar worker, lower-white-collar worker, blue-collar worker, other (unemployed, entrepreneur, student and pensioner) and unknown SES, as described previously [6,20].

### Follow-up data

Data on recurrent vascular events and mortality were obtained from the Care Register for Health Care, from the National Institute for Health and Welfare, Finland, and from Statistics Finland, as described before [1]. Endpoints of interest were as follows: (1) all-cause mortality; (2) composite endpoint including fatal/nonfatal recurrent stroke of ischemic or hemorrhagic origin and transient ischemic attack (TIA), and (3) composite endpoint of any fatal/nonfatal vascular event including cardiac events including ACS, cardiac death and other cardiac events as well as peripheral arterial events, while excluding recurrent stroke of ischemic or hemorrhagic origin and TIA. Follow-up time started from the index stroke and ended on December 31st, 2011, on the date of occurrence of an endpoint of interest, or on the date of death, whichever occurred first [1].

We used the individually unique personal identification codes of Finns to link our data to medication records of the Drug Prescription Register kept by the Social Insurance Institution of Finland. Data on the use of antihypertensive medication was therefore gathered retrospectively, similarly to other studies carried out in Finland and Sweden [21,22]. All purchases used in the treatment of hypertension within anatomical therapeutic chemical (ATC) classes [23] listed by the Finnish Current Care Guideline were included. Consequently, the following ATC codes were used to identify antihypertensive medication: C02 (antihypertensive agents), C03 (diuretic agents), C07 (beta-blocking agents), C08 (calcium channel blockers) and C09 (agents acting on the renin–angiotensin system).

Antihypertensive treatment was indicated following universally accepted goals and was based on both national and international guidelines at the time of inclusion. The general target was SBP of $<$140 mmHg and DBP of $<$90 mmHg throughout the study period. The first Finnish guidelines came in 2001 and recommended SBP $<$140 mm Hg and DBP $<$80 mmHg in patients with diabetes and SBP $<$130 mmHg and DBP $<$80 mmHg in patients with proteinuria [24,25]. Patients were regarded to have an indication for antihypertensive treatment if they had at least two purchased prescriptions after admission to the hospital due to index stroke. The rates of purchased prescriptions are considered as accurate measures of the use of antihypertensive medication in a closed pharmacy system, such as in Finland, especially when the numerous prescriptions are measured at several points in time [26]. A physician writes all prescriptions in Finland, providing the patient with access to the medicine equal to a maximum use of 3 months at once. Usage was defined as the proportion of follow-up time covered by purchased prescriptions of antihypertensive medication, calculating the number of prescriptions needed and consequently comparing that to the number of prescriptions purchased over the entire follow-up period using the Proportion of Days Covered method [27]. We defined usage thresholds of $<$30% (low usage), 30–80% (intermediate usage) and $>$80% (high usage), corresponding with yearly medication purchases of none to 1, 2 and 3 or more [21,26,28]. Patients without any purchased prescriptions were considered as non-users. Individuals who only had one purchase over the whole follow-up period were removed from the analyses, as determining the indication was impossible.

### Standard protocol approvals, registrations and patient consents

We coded all data anonymously in the study database. The local ethics committee approved the study protocol. Informed consent from patients in our cohort was not needed according to Finnish legislation because we did not contact patients or their caregivers.

### Statistical analyses

We performed statistical analyses with IBM SPSS Statistics, version 22.0 (SPSS Inc., IBM, Armonk, NY) and the computer environment R (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2018). A $P$ value of $<$0.05 was considered statistically significant.

Kaplan–Meier curves with Log rank statistics allowed univariate comparison of the risks of endpoint events between usage groups.

First, we used Cox regression model to obtain hazard ratios (HRs) and their corresponding confidence intervals (CIs) as adjusted measures of rate ratios of mortality to compare the different subgroups of use of antihypertensive medication, with non-users as the

reference category. We identified potential confounders from previous literature [1,3,11], and consequently adjusted for age, sex, types 1 and 2 diabetes mellitus, cigarette smoking, heart failure, pre-existing hypertension, dyslipidemia, heavy drinking, contraceptive pill use, modified TOAST classification, NIHSS at admission and prior use of antihypertensive medication. In order to create both comparable and powerful groups for multivariate analysis, thresholds were limited to three groups: non-users, low-intermediate usage and high usage. Proportionality assumption was checked with no violations observed. We did subgroup analyses grouping typical older-onset stroke causes and typical young-onset stroke causes as described before. We also performed a sensitivity analysis on the main outcome including only patients with pre-existing diagnosis of hypertension.

Second, to jointly assess the rate ratios of recurrent stroke or TIA and vascular events other than stroke among different subgroups of use of antihypertensive medication, we used a marginal Cox regression model for multiple outcomes [29]. The rate ratios were adjusted for confounding using the same variables as the Cox regression model assessing the rate ratios of mortality. Proportionality assumptions were checked with no violations observed. Subgroup analyses for old- and younger onset causes of stroke were carried out.

Finally, we calculated adjusted absolute risks (AR), absolute risk reduction (ARR), and number needed to treat (NNT) for each endpoint in the entire cohort by using a logistic regression model, while adjusting for the confounders mentioned before.

## Results

Of the 1,008 patients enrolled in the HYSR, 10 were lost to follow-up (could not be linked to registries), four patients were excluded due to false primary diagnosis and 24 patients (median NIHSS 17.5) died within 30 days from the index stroke. After further exclusions, 936 patients were included in the analyses (Supplementary Figure I). Patients were followed for a median of 8.3 years (interquartile range 5.2–12.5), corresponding with a total of 8084.7 patient-years.

Baseline characteristics appear in Table 1. Of our study population, 40.5% were non-users, 7.8% had low use, 11.8% had intermediate use and 40.0% had high use of antihypertensive medication. Regarding sex differences, 34.3% of women and 43.3% men had high usage, whereas 47.1% of women and 36.5% of men were non-users (Supplementary Figure IIA). Of the patients with history of hypertension, 75.7% had high use of antihypertensive medication. However, 9.0% of hypertension patients were non-users (Supplementary Figure IIB). The proportion of high use slightly decreased with rising socio-economic status, while proportions of high use were the highest among those with unknown socio-economic status (Supplementary Figure III). There were larger proportions of intermediate and high usage with increasing age (Supplementary Figure IVA). Multiple cardiovascular risk factors (type 1 diabetes mellitus, congestive heart failure, dyslipidemia and obesity) were significantly associated ($P < 0.001$) with high usage, while smoking and alcohol abuse were not. Furthermore, proportions of patients using antihypertensive medication prior to their stroke were increasing among patients with higher usage of antihypertensives after their stroke (Supplementary Figure V).

Patients with older-onset stroke causes had a higher proportion of high usage of antihypertensives than patients with young-onset stroke causes (Supplementary Figure IVB). Similar associations emerged when assessing different etiologies separately for groups with and without hypertension (Figure 1). Proportions of high usage were higher for increasing baseline blood pressure values (Supplementary Figure VI).

Of all classes of antihypertensive medication assessed, agents acting on the renin-angiotensin system (ATC class C09) were used in 53.2% of the patients included and were therefore the most commonly used class of antihypertensive medication. Combinations of two classes of antihypertensive medication were used by 15.8% of the patients, while 47.9% used three or more classes of antihypertensive medication. An overview of crude numbers of the endpoints among users of each type of antihypertensive class is presented in Supplementary Table I.

Of all patients, 15.6% died, 17.1% experienced a recurrent stroke or TIA and 17.5% experienced a recurrent vascular event other than stroke during follow-up. Univariate comparison of the risks of endpoint events between different antihypertensive usage groups are shown in Figures 2–4. Numbers of patients at risk for each analysis appear in Supplementary Table II. Absolute risks, relative risks and numbers needed to treat over time are shown in Supplementary Table III. Compared to non-users, low-intermediate usage and high usage were associated with lower mortality in the fully adjusted Cox Regression model (Table 2). Risks of recurrent stroke or TIA were lower for low-intermediate and high

**Table 1.** Selected baseline characteristics of the study population ($n = 936$) stratified by antihypertensive usage during follow-up.

| | Non-users $n = 379$ | Low usage $n = 73$ | Intermediate usage $n = 110$ | High usage $n = 374$ | Total $n = 936$ |
|---|---|---|---|---|---|
| Age | 41.0 (33.0–46.0) | 42.0 (34.0–47.0) | 45.0 (40.0–47.0) | 45.0 (42.0–48.0) | 44.0 (37.0–47.0) |
| Sex (male) | 214 (56.5) | 46 (63.0) | 72 (65.5) | 254 (67.9) | 586 (62.6) |
| Risk factors | | | | | |
| Active malignancy | 8 (2.1) | 0 (0.0) | 0 (0.0) | 2 (0.5) | 10 (1.1) |
| Atrial fibrillation | 10 (2.6) | 1 (1.4) | 1 (0.9) | 23 (6.1) | 35 (3.7) |
| Cigarette smoking | 163 (43.0) | 38 (52.1) | 42 (38.2) | 170 (45.4) | 413 (44.1) |
| Congestive heart failure | 6 (1.6) | 2 (2.7) | 2 (1.8) | 34 (9.1) | 44 (4.7) |
| Coronary heart disease | 13 (3.4) | 2 (2.7) | 5 (4.5) | 25 (6.7) | 45 (4.8) |
| Dyslipidemia | 188 (49.6) | 49 (67.1) | 69 (62.7) | 262 (70.1) | 568 (60.7) |
| Family history of stroke | 47 (12.4) | 5 (6.8) | 13 (11.8) | 54 (14.4) | 119 (12.7) |
| Heavy drinking | 53 (14.0) | 15 (20.5) | 16 (14.5) | 46 (12.3) | 130 (13.9) |
| History of TIA | 23 (6.1) | 3 (4.1) | 10 (9.1) | 45 (12.0) | 81 (8.7) |
| Hypertension | 34 (9.0) | 14 (19.2) | 44 (40.0) | 287 (76.7) | 379 (40.5) |
| Myocardial infarction | 6 (1.6) | 3 (4.1) | 3 (2.7) | 19 (5.1) | 31 (3.3) |
| Type 1 diabetes mellitus | 5 (1.3) | 1 (1.4) | 3 (2.7) | 34 (9.1) | 43 (4.6) |
| Type 2 diabetes mellitus | 9 (2.4) | 1 (1.4) | 6 (5.5) | 40 (10.7) | 56 (6.0) |
| Obesity | 13 (3.4) | 9 (12.3) | 11 (10.0) | 70 (18.7) | 103 (11.0) |
| Oral contraceptive use | 43 (26.1)[a] | 7 (25.9)[a] | 6 (15.8)[a] | 6 (5.0)[a] | 62 (17.7)[a] |
| Peripheral artery disease | 1 (0.3) | 0 (0.0) | 4 (3.6) | 12 (3.2) | 17 (1.8) |
| Prior use of antihypertensives | 32 (8.4) | 12 (16.2) | 25 (22.7) | 218 (58.4) | 287 (30.7) |
| Stroke characteristics | | | | | |
| Infarct size[b] | | | | | |
| Small | 147 (38.8) | 37 (50.7) | 45 (40.9) | 191 (51.1) | 420 (44.9) |
| Medium | 113 (29.8) | 23 (31.5) | 35 (31.8) | 90 (24.1) | 261 (27.9) |
| Large anterior | 68 (17.9) | 7 (9.6) | 13 (11.8) | 52 (13.9) | 140 (15.0) |
| Large posterior | 51 (13.5) | 6 (8.2) | 17 (15.5) | 41 (11.0) | 115 (12.3) |
| Localization | | | | | |
| Anterior | 196 (51.7) | 36 (49.3) | 49 (44.5) | 207 (55.3) | 488 (52.1) |
| Posterior | 173 (45.6) | 33 (45.2) | 54 (49.1) | 151 (40.4) | 411 (43.9) |
| Both anterior and posterior | 10 (2.6) | 4 (5.5) | 7 (6.4) | 16 (4.3) | 37 (4.0) |
| Multiple territories | 13 (3.4) | 5 (6.8) | 6 (5.5) | 22 (5.9) | 46 (4.9) |
| Stroke severity (NIHSS at admission) | 3.0 (1.0–7.0) | 3.0 (1.0–6.0) | 2.0 (1.0–5.0) | 3.0 (1.0–5.0) | 3.0 (1.0–6.0) |
| Stroke etiology (modified TOAST) | | | | | |
| Large artery atherosclerosis | 19 (5.0) | 3 (4.1) | 8 (7.3) | 40 (10.7) | 70 (7.5) |
| High-risk sources of cardioembolism | 16 (4.2) | 5 (6.8) | 8 (7.3) | 56 (15.0) | 85 (9.1) |
| Small-vessel occlusion | 12 (3.2) | 2 (2.7) | 17 (15.5) | 106 (28.3) | 137 (14.6) |
| Other causes | 123 (32.5) | 18 (24.7) | 29 (26.4) | 78 (20.9) | 248 (26.5) |
| Non-ESUS cryptogenic | 100 (26.4) | 27 (37.0) | 29 (26.4) | 47 (12.6) | 203 (21.7) |
| ESUS | 109 (28.8) | 18 (24.7) | 19 (17.3) | 47 (12.6) | 193 (20.6) |

Data are *n* (%) or median (interquartile range). TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale; TOAST: Trial of Org 10172 in Acute Stroke Treatment; ESUS: embolic stroke of undetermined source

[a]Within female patients. [b]The size of a small infarct was a $\leq$1.5 cm lesion in the anterior or posterior circulation, or no visible lesion. A medium infarct was a lesion in the cortical superficial branch of the anterior cerebral artery, middle cerebral artery, posterior cerebral artery, or in a deep branch of middle cerebral artery or posterior cerebral artery, or lesion in internal border zone territories. A large anterior infarct was a lesion involving complete territory of anterior cerebral artery or middle cerebral artery or lesion involving $>$1 arterial territory, and a large posterior infarct a $>$1.5 cm lesion involving brain stem or cerebellum or involving complete territory of posterior cerebral artery together with border zone territories.[1]

usage, while low-intermediate and high usage were associated with higher risks of vascular events other than stroke in the fully adjusted Cox regression model (Table 3). In the sensitivity analysis including only patients with preexisting diagnosis of hypertension, the main results were consistent (Supplementary Table IV).

Compared to non-users, low-intermediate usage and high usage were associated with lower mortality in the fully adjusted Cox regression models in patients with older-onset causes and young-onset causes of their stroke (Table 2).

Low-intermediate usage was not associated with lower risk of recurrent stroke or TIA, while high usage was associated with lower risk of recurrent stroke or TIA in patients with older-onset causes. In patients with young-onset causes, low-intermediate and high usage were associated with lower risk of recurrent stroke or TIA (Table 3).

The use of antihypertensive medication was not associated with lower risks of other recurrent vascular event among patients with older-onset stroke causes and was even associated with higher risks of other recurrent vascular event in patients with young-onset stroke causes (Table 3).

## Discussion

The main findings of our study were the suboptimal usage of antihypertensive medication in one-third of

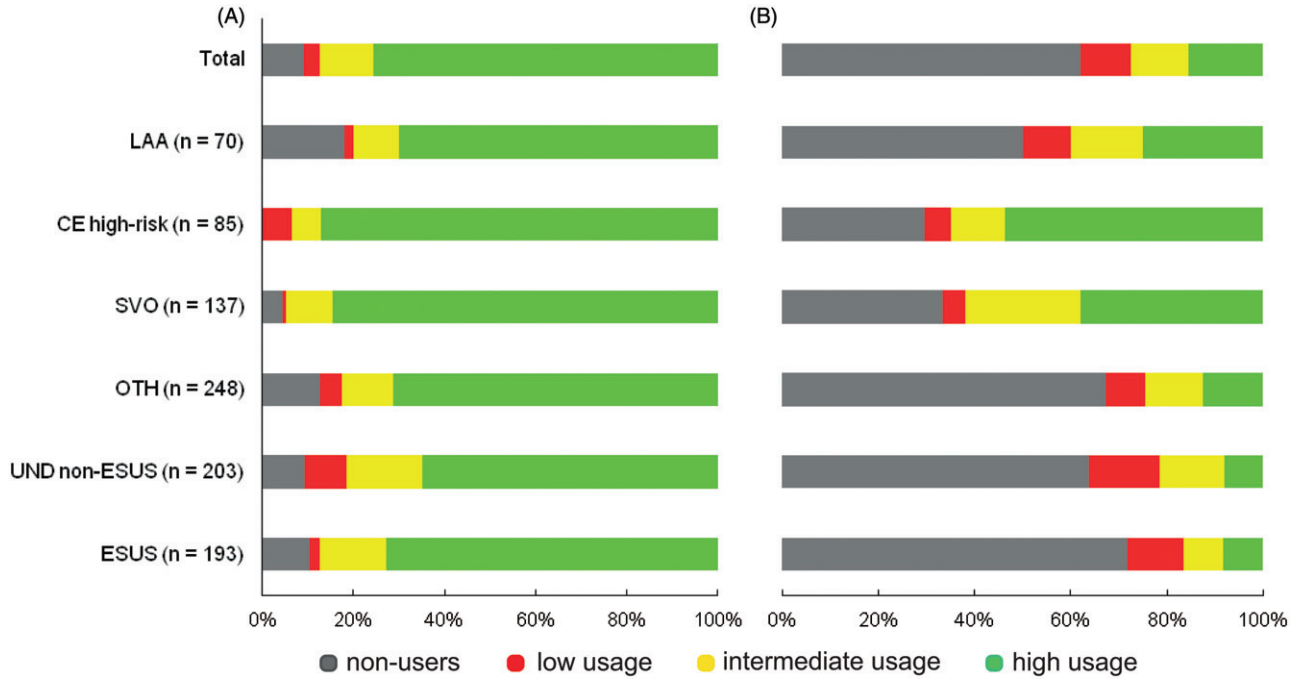


**Figure 1.** Association between modified TOAST categories and use of antihypertensive medication for patients (A) with and (B) without hypertension

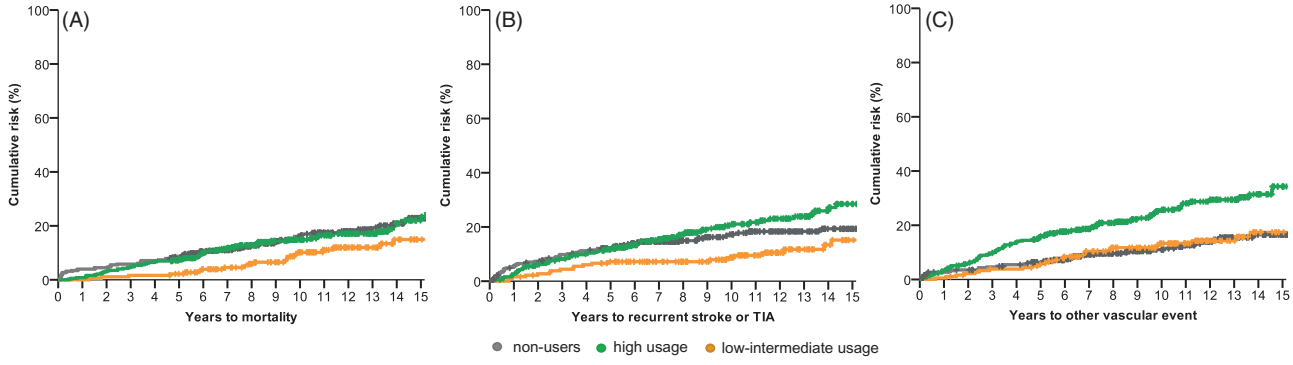


**Figure 2.** Kaplan Meier curves of the study population for (A) all-cause mortality (B) recurrent stroke or TIA and (C) other recurrent vascular event

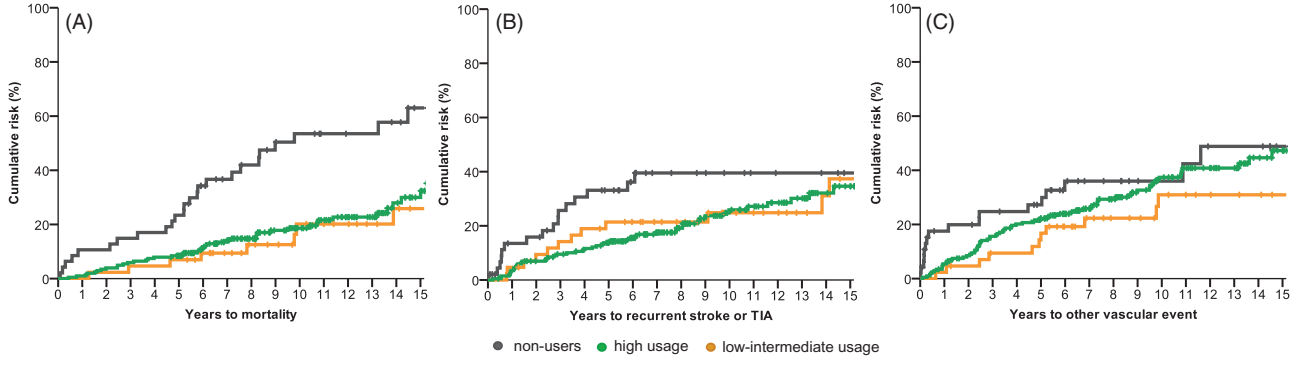


**Figure 3.** Kaplan Meier curves of patients with older-onset causes of their stroke for (A) all-cause mortality (B) recurrent stroke or TIA and (C) other recurrent vascular event

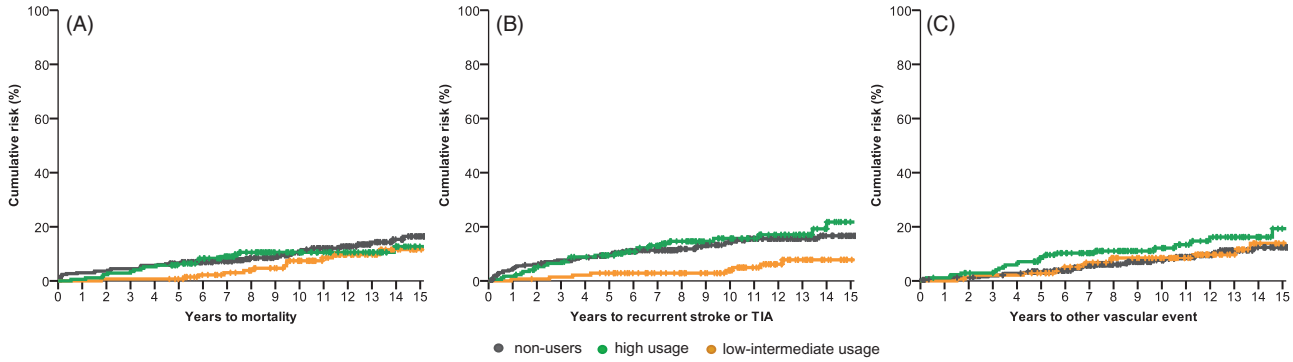


**Figure 4.** Kaplan Meier curves of patients with young-onset causes of their stroke for (A) all-cause mortality (B) recurrent stroke or TIA and (C) other recurrent vascular event

**Table 2.** Fully adjusted hazard ratios of all-cause mortality, non-users as reference category.

| | HR | 95% CI | *p* |
|---|---|---|---|
| Study population ($n = 936$) | | | |
| Non-users | 1 | NA | NA |
| L-I | 0.40 | 0.22–0.65 | <.001 |
| H | 0.25 | 0.15–0.42 | <.001 |
| Older-onset stroke causes ($n = 292$) | | | |
| Non-users | 1 | NA | NA |
| L-I | 0.26 | 0.11–0.62 | .002 |
| H | 0.18 | 0.09–0.35 | <.001 |
| Young-onset stroke causes ($n = 644$) | | | |
| Non-users | 1 | NA | NA |
| L-I | 0.38 | 0.19–0.79 | .010 |
| H | 0.37 | 0.16–0.82 | .015 |

HR: hazard ratio with non-users as the reference category; CI: confidence interval; H: high usage; L-I: low-intermediate usage; NA: not applicable; TIA: Transient Ischemic Attack.

**Table 3.** Fully adjusted hazard ratios of recurrent TIA/stroke and other recurrent vascular events, non-users as reference category.

| | | HR | 95% CI | *p* |
|---|---|---|---|---|
| *Study population* ($n = 936$) | | | | |
| Recurrent stroke or TIA | Non-users | 1 | NA | NA |
| | L-I | 0.31 | 0.18–0.53 | <.001 |
| | H | 0.30 | 0.19–0.46 | <.001 |
| *Other recurrent vascular event* | Non-users | 1 | NA | NA |
| | L-I | 2.02 | 1.03–3.95 | .040 |
| | H | 2.03 | 1.26–3.26 | .004 |
| Older-onset stroke causes ($n = 292$) | | | | |
| Recurrent stroke or TIA | Non-users | 1 | NA | NA |
| | L-I | 0.50 | 0.22–1.14 | .099 |
| | H | 0.28 | 0.15–0.52 | <.001 |
| Other recurrent vascular event | Non-users | 1 | NA | NA |
| | L-I | 0.81 | 0.27–2.47 | .714 |
| | H | 1.51 | 0.67–3.44 | .324 |
| Young-onset stroke causes ($n = 644$) | | | | |
| Recurrent stroke or TIA | Non-users | 1 | NA | NA |
| | L-I | 0.20 | 0.09–0.46 | <.001 |
| | H | 0.40 | 0.21–0.79 | .008 |
| Other recurrent vascular event | Non-users | 1 | NA | NA |
| | L-I | 3.68 | 1.41–9.65 | .008 |
| | H | 1.47 | 0.74–2.91 | .268 |

HR: hazard ratio with non-users as the reference category; CI: confidence interval; H: high usage; L-I: low-intermediate usage; NA: not applicable; TIA: Transient Ischemic Attack.

all users after IS at young age and the lower risk of mortality and recurrent stroke or TIA in antihypertensive users compared to non-users after adjustment for relevant confounders. Specific guidelines on antihypertensive medication use after young IS are lacking. However, our results may motivate doctors and patients in gaining better usage of antihypertensive medication, since better usage was associated with more favorable outcome in this study.

In our study, higher proportion of antihypertensive use and better usage appeared with increasing age, which is in accordance with previous studies on general population [10,30,31]. We also found presence of cardiovascular risk factors to be associated with higher frequency of antihypertensive users with higher usage, corresponding with earlier findings and suggesting that patients with severe clinical conditions are more willing to follow a therapeutic regimen [32,33]. We did not find an association between lower SES and lower use of antihypertensive medication, which is in accordance with previous research [34].

We found usage of antihypertensive medication to be associated with mitigated risks of all-cause mortality and recurrent stroke or TIA when compared with non-users, corresponding with significant risk reduction during follow-up. This association was independent of demographics, preexisting hypertension, prior use of antihypertensive medication, other comorbidities and stroke subtype, underlining the importance of antihypertensive medication in the secondary prevention of stroke in young adults. Adjusted absolute risk reduction of mortality after 1 year of follow-up was 32.9% in high-using patients compared to non-users. Over-all risk of mortality after 1 year of follow-up was found to be 4.7%, which might be reduced by the use of antihypertensive medication after stroke at young age [35]. Previous studies found significant differences

between low and high adherence to antihypertensive medication benefitting the patients with high adherence regarding risks of any recurrent cardiovascular event. However, these studies included an older population of patients diagnosed with hypertension, which might be the reason that we did not find lower risks for recurrent vascular events among any users of antihypertensive medication [32,36]. Higher risks of recurrent events other than stroke or TIA among users of antihypertensive medication might have several explanations. First, high-using patients might have more cardiovascular risk factors and are therefore willing to follow a therapeutic regimen, but are at a initial higher risk of vascular events. Second, these patients might have a treatment-resistant early-onset diagnosis of hypertension or secondary hypertension, causing the higher risk of other recurrent vascular events. However, absolute numbers of events are low for other recurrent vascular events, and thus caution is warranted when interpreting this finding.

Our study also showed significant differences between patients grouped into young-onset and older-onset causes. Antihypertensive users with both young-onset and older-onset causes of their stroke had lower risks of all-cause mortality than non-users, underlining the importance of antihypertensive medication as secondary prevention after stroke. The risk of recurrent stroke or TIA was lower for high usage compared to non-users in patients with older-onset causes of their stroke, while the risk of recurrent TIA or stroke was not lower for low-intermediate usage. This corresponds with previous findings of higher risks of recurrent (fatal) stroke with a stepwise decline in usage in an older population with high prevalence of these etiologies [21]. Consequently, this strengthens the view that to reduce the risk of a recurrent stroke or TIA in patients with LAA, CEH or SVO, high usage of antihypertensive medication might be essential. However, these patients may have been exposed to the beneficial effects of other (secondary) preventive therapies, an aspect we were not able to analyze in this study. In addition, we were unable to reliably analyze specific TOAST subgroups due to low numbers and thus our data are not directly generalizable to specific etiologies. Both low-intermediate and high-adherent antihypertensive users with young-onset causes of their stroke were at lower risk of experiencing a recurrent stroke or TIA compared with non-users. However, the risk of other recurrent vascular event was not lower for patients with older-onset stroke causes, and even higher among patients with young-onset stroke causes compared to non-users. This might be explained by higher use of antihypertensive medication among patients with more cardiovascular risk factors, or among patients with other indications for antihypertensive medication, which are not included in this study.

The strengths of our study include a large non-selected study population with long follow-up, multiple endpoints and registry-based source-data verified outcome data, with only 0.1% loss to follow-up. In addition, our registry contains virtually all young stroke patients from the HUH catchment area [11]. Therefore, our study population is a good sample to represent the population of young stroke patients. Furthermore, the data obtained from the Drug Prescription Register can be considered as accurate measures of the usage of medication, as Finland has a closed pharmacy system and data on prescriptions are kept at several points in time and are available for clinicians and researchers [28]. As we used marginal Cox regression model for multiple outcomes to assess the outcomes other than mortality, there were no competing risks in the analyses, as patients could experience both endpoints in the model used. Furthermore, the analysis assessing rate ratios of mortality among different usage groups of antihypertensive medication was ran separately, taking all causes of mortality into account. Consequently, there were no competing risks for mortality as well.

This study also has limitations. First, the endpoints of interest in this study were registry-based, leaving a possibility of selection bias and misclassification of events. The positive predictive value and sensitivity of the registries used to obtain data on the endpoints of interest have been fairly good for both fatal as non-fatal cardiovascular events, although validation of recurrent strokes is lacking for patients aged 15–25 years [37–39]. Furthermore, the events of interest of the present study virtually always lead to hospitalization in Finland. Second, the diagnostic and etiologic workup, including the use of MRI and vessel imaging, has evolved during the inclusion period of the cohort. By excluding patients with only one prescription, the proportion of non-users or low usage might have been underestimated. In addition, it is important to stress that although the data on prescriptions with a purchase of antihypertensive medication is objective and are collected routinely, they do not measure the actual intake of these medications, leading to a possible

underestimation of the proportion of low usage, intermediate usage or even non-users [21]. However, high concordance between prescriptions and the golden standard of measuring medication adherence, the Medication Event Monitoring System, indicates that the rate of purchased prescriptions is in line with the rate of consuming by the patients [40]. As this study was registry-based, indications other than hypertension for prescribing antihypertensive medication could not be determined, which might have influenced our results. Moreover, clinical data on the indication of antihypertensive medication during the follow-up period was not available as patients did not have clinical follow-ups during the follow-up period in this registry-based study. Therefore, we were not able to determine whether a patient lost indication for antihypertensive medication during the follow-up period and could consequently not assess any side effects that lead to discontinuation. In addition, as medication usage is not the same as optimal blood pressure control, differences in blood pressure control in the same usage categories might have affected the results. However, as this study is registry-based, data on blood pressure control was not available. Finally, possible reasons for high adherence include high stroke severity, as medication might be provided by the hospital. However, high stroke severity might as well lead to lower adherence, as secondary prevention could have been stopped in palliative care settings. To fully assess if NIHSS influenced the results, we ran the analyses with and without NIHSS as a covariate, after which the results did not differ significantly, suggesting that NIHSS score did not account for the differences in outcomes among users compared to non-users of antihypertensive medication.

## Disclosure statement

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